

Studies on 5-Bromo-4,7-dimethylindene, an Intermediate in the Synthesis of 6-Bromo-5,8-dimethylisoquinoline

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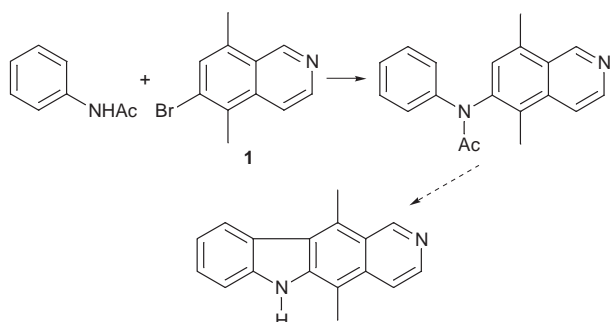
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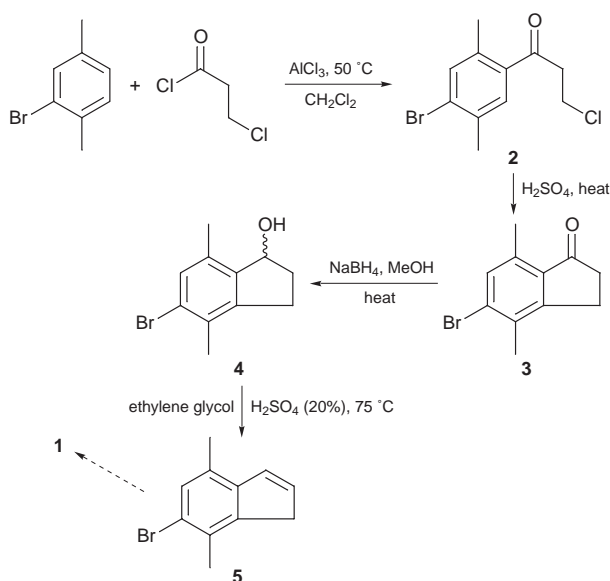
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1999, 1970–1979

We report the complete characterisation of all the precursors of 6-bromo-5,8-dimethylisoquinoline *via* the synthesis of Miller and Moock, and the synthesis of 6-bromo-4,7-dimethyl-2-(5'-Bromo-4',7'-dimethyl)-2',3'-dihydro-1'*H*-inden-1'-yl)-1*H*-indene.

The synthesis of 6-bromo-5,8-dimethylisoquinoline **1** was disclosed some years ago by Miller and Moock as part of a synthesis of ellipticine (Scheme 1) and it was claimed to be an intermediate for the general synthesis of ellipticines¹ but no further data were, subsequently, published, nor does it appear to have been used for the synthesis of other ellipticines. On account of the possible general application of the route and because the properties of none of the compounds **2–5** were reported before, we have now isolated and fully characterised the compounds up to the indene **5** (Scheme 2).

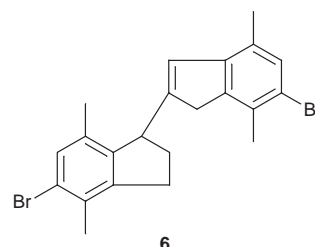


Scheme 1



Scheme 2

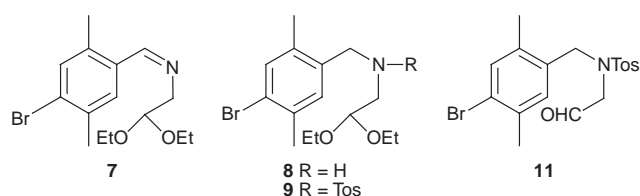
When dehydration of the alcohol **4** was performed under the conditions of Miller and Moock (H₂SO₄–ethylene glycol)¹ the indene was obtained in 64% yield. However if alternatively the dehydration of the alcohol **4** was carried out using TFA, the product, in our hands, was not the indene **5**, as claimed previously,² but the dimer **6**. Several conditions have been described previously for the dehydration of indanols.^{3,4} However the formation of this type of dimer was also observed during the acid-catalysed dimerisation of indenenes when treated with 5% TFA in chloroform,⁴ with 85% phosphoric acid⁵ or with 48% H₂SO₄.⁶ Recently it was reported⁷ that the best conditions for the dehydration of 4-methylindan-1-ol, under which the yields of the dimer or the indene could be maximised, were the use of benzene with toluene-*p*-sulfonic acid. The formation of the dimer **6** can be rationalised by the previously proposed mechanism for similar compounds.^{5,7}



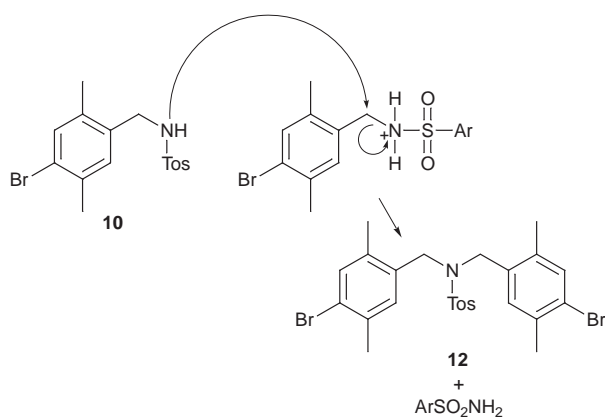
The mass spectrum of **6** showed the characteristic pattern for a compound with two bromine atoms with low intensity molecular ions at *m/z* 448 (6%), 446 (12%), 444 (6%) and two ions at 225 (86%) and 223 (96%) owing to cleavage into two simple units. The ¹H NMR spectrum showed four methyl signals and two aromatic singlets due to 5 and 6'-H, and an AB quartet centred at δ3.17 (1-CH₂), a broad doublet at δ4.30 (1'-H) and a singlet at δ6.33 due to the 3-H.

As an alternative to Miller and Moock's synthesis of the isoquinoline¹ (global yield 69%) and to the synthesis *via* Pomeranz–Fritsch cyclisation⁸ (global yield 13%) we tried to improve the yield using the sulfonamide modification of the Pomeranz–Fritsch cyclisation.⁹ In the event, however, the pathway **7** → **8** → **9** followed by attempted acid-catalysed cyclisation of **9** gave no isoquinoline but instead the products **10–12** the structures of which were elucidated from their spectroscopic properties. The sulfonamide **12**, with molecular ions at *m/z* 567 (1%), 565 (2%) and 563 (1%), indicated the presence of two bromine atoms and the pattern is maintained for ions resulting from cleavage of the tosyl group at *m/z* 412 (15%), 410 (31%) and 408 (18%).

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Although aldehyde **11** may be an intermediate in the cyclisation of the *N*-tosylacetals of the type **9**, it was also obtained previously, when lack of reactivity inhibited the cyclisation.⁹ The same authors suggest⁹ possible mechanisms of formation of a compound analogous to **10**. The formation of compound **12** may be envisaged as the attack of sulfonamide **10** on its conjugated acid as shown in Scheme 3.



Scheme 3

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Techniques used: ¹NMR, mass spectrometry, elemental analysis

References: 9

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